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Dear Examiner Ware:

Following is some information that we thought may be helpful in organizing the interview scheduled for 2:00 today. We are also providing a new proposed claim set which we believe to be distinguished from the teachings of the '951 patent and which places the claims in the order of highest priority to the inventor. Dr. Cubicciotti and I look forward to discussing this case with you later today.

Kathleen A. Tyrrell

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PENDING 112 REJECTION:
With respect to the pending § 112, second paragraph rejection, the phrase that has been suggested to be indefinite does not even appear in the claim anymore. The phrase that is suggested to be unclear is "a drug bound to a synthetic receptor selected to bind said drug by a method selected from . . . "

Claim 14 is drawn to:
A prodrug complex comprising a drug specifically bound to a synthetic receptor selected to bind to said drug via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug, wherein said synthetic receptor is selected by a method selected from the group consisting of combinatorial selection, monoclonal antibody selection and antibody engineering, wherein said drug preferentially dissociates from the synthetic receptor and binds to a pathophysiologic receptor following administration of the prodrug complex to an organism.

Claim 15 is drawn to:
The prodrug complex of claim 14 wherein a biologic or biocompatible structure is attached to the prodrug complex.

This rejection also appeared in the Office Action mailed November 7, 2000 and was addressed by amendment of the claims in the response filed February 7, 2001. Further amendments to claims in the Preliminary Amendment filed with the request for continued prosecution did not introduce this phrase back into the claim.

With respect to the pending § 102 rejection over Morgan Jr. et al. (U.S. Patent 5,106,951) we are providing the following chronology

Date of Office Action	Examiner's Reasons for Rejection and Comments offered to Applicant's previous response	Applicant's Response
5/23/00	'951 discloses drug/carrier complexes and method for administering drug via the drug carrier complex where drug binds polymeric complex to form a prodrug complex capable of allowing drug dissociation from polymeric carrier so that drug retains its ability to bind to target. 1. Abstract; C4, L43-C5, L25; C8,L30-40;C18, L43-48) cited as teaching conjugate to preferentially bind "pathophysiologic receptor" 2. C4,L43-50 cited as teaching that drug-conjugate is not exposed to derivatization conditions compromising potency which is equated with the drug being immobilized and protected from metabolism thus increasing half-life 3. C7,L10-19 and30-37 cited as disclosing that targeting proteins may be attached to the conjugate 4. C10, L62-66 cited as disclosing that carriers may also bind more than one	Claim 13 (the ONLY claim to immobilized prodrugs) was amended to clarify that the complex is immobilized to a biologic or biocompatible structure; arguments and evidence as to the Examiner's interpretation of "immobilized" being different to those of skill in the art were also presented; Claims 14-29 were amended to recite methods for identifying synthetic receptors. Differences between function and method of identifying drug targeting synthetic receptors used in this invention and cell targeting antibodies and csDBM designed to have opposite functionalities and complementary structure to drug molecule of '951 patent were highlighted.

	drug molecule Examiner also stated that methods used to identify conjugates are considered patentably distinct as they are intended use limitations and that antibodies of '951 would be identifiable by instant methods.	
11/7/2000	Rejection presented is identical to that of 5/23/00 Office Action; claims were also rejected under 103 for identical reasons; however, the Examiner stated that methods used to identify conjugates were NOT considered patentably distinct In response to Applicant's arguments, Examiner submitted that there was more than one meaning for term "immobilized" and as such language was insufficient to overcome the rejection of claims 13-29. Specifically, binding of the drug to the conjugate was considered to be "tied together" meeting the definition of immobilized. Amendments to claims 14-29 which are NOT drawn to immobilized prodrugs were not addressed by the Examiner	With respect to claim 13, Applicant requested clarification as to how conjugate of '951 patent could be "tied together" to drug when drug was expressly taught to be a component of the conjugate of the '951 patent. With respect to claims 14-29, Applicant pointed out that Examiner failed to address arguments presented in last response. Applicant also clarified that these claims were drawn not only to complexes but also to methods for producing complexes. Applicant also clarified that methods in the claims were not related to use of the complex but rather production of complex. Applicant clarified why cell targeting antibodies of Morgan would not be identifiable via the methods of identifying a synthetic receptor which binds to a drug
3/02/01	Advisory Action stated that amendment did not place case in condition for allowance because "claims do not	Applicant called Examiner on 4/10/01 to request clarification as to how '951 patent pertained to claims 14-

	require insolubility to be immobilized". No mention of claims 14-29 which do not pertain to immobilized complexes was made	29. Examiner clarified that the antibody of '951 patent was similar in function to the synthetic receptor the claimed invention and that a structural difference, not a difference in production, was needed to distinguish the complexes. Applicant clarified that invention did not require csDBM between synthetic receptor and drug. Examiner indicated that pending claims were not limited in this manner.
4/24/01	In the Summary of the Telephone Interview the examiner clarified that "the antibody of Morgan Jr. is considered to be the "synthetic receptor"", that there was no claim limitation that there was nothing between the synthetic receptor and the drug of this invention, and that the process limitations were anticipated by Morgan et al. because Morgan used purified antibodies.	Applicant filed a CPA and preliminary amendment adding to claims the limitation that the selected drug was specifically bound to the synthetic receptor via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug. Applicant identified multiple sites in application where criticality of this limitation to the invention was taught.
6/5/01	Rejection presented is identical to that of 5/23/00 and 11/7/00 Office Actions; however - Now the Examiner suggests that the csDBM-antibody complex of '951 meets the requirement of a synthetic receptor	Applicant requested a Telephone Interview in an effort to further this prosecution - draft claims to be considered during this interview are provided herewith

Claims we would like to have considered and discussed during the ~~Telephone Interview~~

30. A method of producing a prodrug complex comprising:

(a) selecting a drug to be delivered as a prodrug complex;

(b) selecting a synthetic receptor that specifically binds the drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug, wherein the synthetic receptor is selected by at least one of combinatorial selection, in vitro evolution, or selection of antibodies, engineered antibodies, antibody mimics, oligonucleotides or oligosaccharides; and

cyclodextrins

(c) specifically binding the selected drug to the selected synthetic receptor to form a prodrug complex.

31. The method of claim 30 further comprising attaching the prodrug complex to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

32. A method of producing a prodrug complex comprising:

(a) selecting a drug to be delivered as a prodrug complex;

(b) selecting a synthetic receptor that specifically binds the drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug, wherein the synthetic receptor is selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins and polymers comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers; and

(c) specifically binding the selected drug to the selected synthetic receptor to form a prodrug complex.

33. The method of claim 32 further comprising attaching the prodrug complex to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

34. A method of producing a multi-prodrug complex comprising:

(a) selecting at least two drugs to be delivered as a multi-prodrug complex;

(b) selecting at least two synthetic receptors that specifically bind the selected drugs via saturable, noncovalent interaction between the selected drugs and the selected synthetic receptors that can be competitively inhibited by structural analogs of the selected drugs, wherein at least one of the synthetic receptors is selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins, polymers comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers, and products of combinatorial selection, in vitro evolution, or selection of antibodies, engineered antibodies, antibody mimics, oligonucleotides or oligosaccharides; and

(c) specifically binding the selected drugs to the selected synthetic receptors to form a multi-prodrug complex.

35. The method of claim 34 further comprising attaching the multi-prodrug complex to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

36. A method of enhancing delivery of a drug to a pathophysiologic receptor for the drug comprising:

(a) selecting a drug capable of binding to a pathophysiologic receptor;

(b) selecting a synthetic receptor that specifically binds the drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug;

(c) producing a prodrug complex by specifically binding the drug to the synthetic receptor; and

(d) administering the prodrug complex to an organism so that the drug dissociates from the synthetic receptor and binds to the pathophysiologic receptor.

37. The method of claim 36 further comprising attaching the prodrug complex to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

38. A method of enhancing delivery of at least two selected drugs to pathophysiologic receptors for the selected drugs comprising:

(a) selecting at least two drugs capable of binding to pathophysiologic receptors;

(b) selecting synthetic receptors that specifically bind the selected drugs via saturable, noncovalent interaction between the selected drugs and the selected synthetic receptors that can be competitively inhibited by structural analogs of the drugs;

(c) producing a multi-prodrug complex by specifically binding the selected drugs to the selected synthetic receptors; and

(d) administering the multi-prodrug complex to an organism so that the selected drugs dissociate from the synthetic receptors and bind to the pathophysiologic receptors.

39. The method of claim 38 further comprising attaching the multi-prodrug complex to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres,

nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

40. A prodrug complex comprising a drug specifically bound to a synthetic receptor, said prodrug complex being produced by the method of claim 30 or 32.

41. A drug delivery system comprising the prodrug complex of claim 40 attached to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

42. A multi-prodrug complex comprising at least two prodrug complexes, wherein at least one of the prodrug complexes is produced by the method of claim 30 or 32.

43. A drug delivery system comprising the multi-prodrug complex of claim 42 attached to a biologic or biocompatible structure selected from the group consisting of molecules, molecular complexes, microstructures, cells, vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.

44. An immobilized prodrug complex comprising:

(a) a synthetic receptor;

(b) a drug specifically bound to the synthetic receptor via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug; and

(c) a biologic or biocompatible structure to which the synthetic receptor or drug is immobilized.

45. The immobilized prodrug complex of claim 44, wherein the biologic or biocompatible structure is selected from the group consisting of microstructures, cells,

vesicles, microparticles, polymers, gels, matrices, blood forming elements, reticuloendothelial cells, liposomes, microspheres, nanostructures, biopolymers, multimolecular complexes, cell membranes, implants and prosthetic devices.